REMARKS

STATUS OF THE CLAIMS.

Claims 1, 3-21, and 23-25 are pending with entry of this amendment, claims 2 and 22 being cancelled without prejudice.

OBJECTIONS

Claims 2 and 22 were objected to under 37 C.F.R. § 1.75(c) for failing to further limit the subject matter of the claims from which they depended. Office Action, page 2. This objection has been overcome by canceling claims 2 and 22, as suggested by the Examiner.

35 U.S.C. §112, SECOND PARAGRAPH.

Claims 19, 21, 22, and 24 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting "about 20%." Office Action, page 2. Applicants respectfully traverse the rejection.

The rejection is based on the Examiner's contention that the metes and bounds of these claims are unclear because the specification does not set forth any definition or range of what is encompassed by "about 20%." Office Action, page 3. Applicants respectfully submit that the Examiner's position is inconsistent with well-settled case law. In *Verve LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002), for example, the Federal Circuit stated:

> Expressions such as "substantially" are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to "particularly point out and distinctly claim" the invention, 35 U.S.C. §112, and indeed may be necessary in order to provide the inventor with the benefit of his invention. In *Andrew Corp. v. Gabriel Elecs. Inc.*, 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988) the court explained that usages such as "substantially equal" and "closely approximate" may serve to describe the invention with precision appropriate to the technology and without intruding on the prior art. The court again explained in *Ecolab Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367, 60 USPQ2d 1173, 1179 (Fed. Cir. 2001) that "like the term 'about,' the term 'substantially' is a descriptive term commonly used in patent

> claims to 'avoid a strict numerical boundary to the specified parameter,'" quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed. Cir. 1995).

Verve LLC, at 1120. Accordingly, Applicants submit that the use of the term "about" to avoid a strict numerical boundary for a parameter is permitted so long as this usage does not create uncertainty as to whether the claim reads on the prior art. As discussed in detail below, Applicants believe that other elements of the claims fully distinguish the prior art. Thus, the term "about 20%" is sufficiently clear and definite to satisfy § 112, second paragraph. Accordingly, withdrawal of the rejection is respectfully requested.

35 U.S.C. §103(a).

Brown and Smith

Claims 1-16, 20, 23 and 25 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al. (USPN 5,807,522) in view of Smith (PCR Methods and Applications (1992) 2:71-72). Office Action, page 3. This rejection is respectfully traversed.

Of the rejected claims, only claims 1 and 20 are independent. The method of claim 1 employs "a plurality of samples of double-stranded polynucleotide fragments, wherein each sample is derived from a first [i.e., a starting] polynucleotide." According to the method, each sample is amplified to form an amplification product that is "representative of the corresponding first polynucleotide." Target solutions containing the amplification products are then applied to one or more substrates to produce an array of polynucleotides that is representative of the plurality of first polynucleotides. It is important to note that the specifically recited amplification steps consistently produce amplification products that are highly representative of the starting polynucleotides. This feature of the invention facilitates quantitative comparison among hybridization signals produced when the target solutions are arrayed and hybridized with sample polynucleotides. Claim 20 recites an "array of polynucleotides that is representative of a plurality of first polynucleotides."

The three elements of a *prima facie* case of obviousness are: (1) the reference(s) must teach or suggest all of the elements of the claimed invention, (2) there must be some motivation for combining or modifying the teachings of the references to arrive at the claimed invention, and (3) the reference(s) or knowledge in the art must provide a reasonable expectation of success, i.e., a reasonable assurance that the claimed invention would work.

Applicants submit that the Examiner has failed to establish any of the elements of a *prima facie* case of obviousness. The previous Amendment set forth the deficiencies of the obviousness rejection over Smith in view of Brown. That the Examiner now relies on Brown as the primary reference does not change the fact that neither Smith nor Brown, alone or in combination, teaches or suggests a "method for preparing an array of polynucleotides that is representative of a plurality of first polynucleotides" (claim 1) and a polynucleotide array having this feature (claim 20). Thus, the Brown-Smith combination fails to satisfy the first element of a *prima facie* case of obviousness.

With respect to the second element of a *prima facie* case, the Examiner indicates that Applicants previous arguments concerning this element are moot because "the rejection has changed." Office Action, page 7. Applicants had argued that the combination of Smith and Brown failed to provide the specific motivation required for modifying the teachings of these references to arrive at the claimed invention. Applicants respectfully point out that this argument must be given appropriate weight, regardless of whether Smith or Brown is considered to be the primary reference.

In attempting to find the specific motivation required for a *prima facie* case, the Examiner notes that "Brown teaches a method of preparing an array of polynucleotides, including preparing an array of amplified polynucleotides." Office Action, page 4. To be more specific, Brown discloses the use of PCR to "randomly" amplify DNA for robotic spotting on substrates. Brown, col. 16, lines 9-22; col. 17, lines 46-55. However, nothing in Brown teaches or suggests any measures that would produce an amplification product (and, ultimately, target solution) wherein the starting polynucleotide sequences are present in approximately the same proportions as in the starting polynucleotide and thus representative of essentially the entire starting polynucleotide. Brown's reference to "random" PCR amplification indicates that random primers were used, which would not yield amplification products that were as highly representative of the starting polynucleotide as those produced according to the recited method steps. This is, effectively, a teaching away from the type of method recited in the pending claims, and it is well-settled that the Examiner must view the reference as a whole, including any teaching away from the claimed invention. Instead, the Examiner has disregarded this teaching away and viewed Brown as teaching the general notion of amplification to produce DNA for an array. Even if this view of Brown were correct, a generic teaching of that amplification was useful for a specific purpose would not, without

more, motivate one skilled in the art to use ***any*** particular amplification method for that purpose. Furthermore, as will be discussed in detail below, one skilled in the art could not reasonably expect that the particular amplification method would work for that purpose.

The Examiner attempts to find motivation for ignoring Brown's teaching regarding "random amplification" and substituting Smith's ligation-mediated PCR amplification to produce DNA for arrays as follows: "Smith teaches that his PCR products can be used in arraying high-density grids (e.g., polynucleotide arrays) (pg. 26)." Office Action, page 5 Applicant respectfully submit that this misstates Smith's teaching. At page 26, Smith states "it is possible that pools of tagged PCR products from the ends of heterologous DNA segments cloned in YACs or cosmids could be employed for multiplex chromosome walking in clone libraries arrayed in high density grids." Chromosome walking is technique wherein sequences from the end of a clone of interest are labeled and used as probes to identify additional clones that potentially contain flanking sequences. In this way, the sequence information for, e.g., a gene of interest can be extended. Accordingly, Smith teaches using ligation-mediated PCR products to ***probe*** conventionally created DNA arrays. Smith does not teach or suggest arraying ligation-mediated PCR products, as the Examiner states. Accordingly, Applicants submit that the motivation cited by the Examiner is insufficient to satisfy the second element of a *prima facie* case of obviousness.

Turning to the third element of a *prima facie* case, the Examiner states that "Brown specifically teaches applying PCR products to microarray, and therefore, there is no reason to believe that the PCR products of Smith would not be able to be applied to a microarray." Office Action, page 7. Applicants respectfully submit that this rationale would, at best, make it obvious to try the arraying Smith's ligation-mediated PCR products, assuming the other elements of a *prima facie* case were present (which Applicants do not concede). As those skilled in the art readily appreciate, techniques that theoretically ***might*** work, often do not work in practice. In support of this point, Applicants submit the Declaration Under 37 C.F.R. § 1.132 of Dr. Donna G. Albertson. In this Declaration, Dr Albertson explains that, in developing the invention, the inventors tried a different amplification method, namely "shotgun cloning" the P1 or BAC inserts into a DNA sequencing vector, followed by PCR amplification of the ligation mixture. Albertson Declaration, page 2. According to the Examiner's rationale, there is no reason to believe that the PCR products of this method could not be arrayed and used in hybridization reactions. Yet, as Dr. Albertson states,

"hybridization intensities were very low on the spots made from the DNA amplified from the ligation mixtures," rendering this method unsuitable for preparing target solutions for arrays. Albertson Declaration, page 13. Thus, even though this method theoretically ***might*** have been expected to work, in fact, it did not. Dr. Albertson's Declaration establishes that the preparation of target solutions for arrays is not as straightforward as the Examiner contends. Applicants submit that those of skill in this art would be aware that this area is relatively unpredictable and would therefore not view the Brown-Smith combination as providing a reasonable expectation of success.

In summary, Applicants maintain that the Examiner has not established a *prima facie* case of obviousness because the record fails to provide any of the elements of a *prima facie* case. However, even assuming *arguendo* that a *prima facie* case had been established, Applicants submit that Dr. Albertson's Declaration provides evidence of unexpected results, which is a "secondary consideration" sufficient to rebut any *prima facie* case of obviousness.

As stated by the Court of Appeals for the Federal Circuit in *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-663 (Fed. Cir. 2000):

> In order to determine obviousness as a legal matter, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and ***unexpected results***. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. (BNA) 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 877, 27 U.S.P.Q.2D (BNA) 1123, 1128 (Fed. Cir. 1993).
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> Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness. See, e.g., *Loctite*, 781 F.2d at 873, 228 U.S.P.Q. (BNA) at 98 ("Secondary considerations . . .,when present, must be considered."); *Simmons Fastener Corp. v. Ill. Tool Works, Inc.*, 739 F.2d 1573, 1575, 222 U.S.P.Q. (BNA) 744, 746 (Fed. Cir. 1984) ("Only after all evidence of nonobviousness has been considered can a conclusion on obviousness be reached."); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306, 227 U.S.P.Q. (BNA) 657, 662 (Fed. Cir. 1985) ("Just as it is legal error for a district court to fail to consider relevant evidence going to secondary considerations, it may be legal error for a district court to presuppose that all evidence relating to secondary

> considerations, when considered with the other Graham indicia relating to the obviousness/nonobviousness issue, cannot be of sufficient probative value to elevate the subject matter of the claimed invention to the level of patentable invention."). Indeed, in Stratoflex, we said:
>
> > ***Evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.*** It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.
>
> *Stratoflex, 713 F.2d at 1538, 218 U.S.P.Q. (BNA) at 879.* Such evidence "may be sufficient to overcome a prima facie case of obviousness." *In re Beattie*, 974 F.2d 1309, 1313, 24 U.S.P.Q.2D (BNA) 1040, 1043 (Fed. Cir. 1992).

Ruiz v. A.B. Chance Co., 234 F.3d 654, 662-663 (Fed. Cir. 2000).

In the present case, Dr. Albertson's Declaration is submitted to show that there are any number of amplification methods that could have been considered in connection with preparing target solutions for DNA arrays. In theory, any of these methods ***might*** have worked. However, the inventors selected two amplification methods from among the myriad possibilities and found that one worked and one did not. Specifically, Dr. Albertson testifies:

> We . . . investigated . . . techniques aimed at reducing the viscosity of the P1 and BAC DNA target solutions and conveniently producing large amounts of DNA from the genomic clones. There are a wide variety of techniques that would reduce DNA molecular size, which would be expected to reduce target solution viscosity, facilitating spotting. However, to produce useful arrays, each target solution must be representative of the starting polynucleotide from which it was produced. More specifically, each target solution must, when spotted and hybridized with a labeled probe, produce a signal that is essentially the same as the signal obtained from the starting polynucleotide.
>
> We decided to test the following three techniques for producing P1 or BAC DNA target solutions: (1) fragmenting the P1 or BAC DNA using sonication or chemical treatments of the DNA; (2) ligation-mediated polymerase chain reaction (PCR); and (3) "shotgun cloning" the P1 or BAC inserts into a DNA sequencing vector, followed by PCR amplification of the ligation mixture. In advance of these studies,

> we could not predict whether any of these techniques would yield sufficiently representative target solutions. In particular, we could not be sure that the amplification-based techniques would satisfy this requirement, as essentially all of the starting P1 BAC DNA sequences would have to be amplified to essentially the same extent to produce an amplification product (and, ultimately, target solution) in which the P1 or BAC DNA sequences were present in approximately the same proportions as in the starting P1 or BAC DNA.
>
> Prior to carrying out these studies, my expectation was that the third approach, shotgun cloning, followed by PCR, was the most likely to give satisfactory results. In fact, as detailed below, this approach failed absolutely. However, the second approach, based on ligation-mediated PCR, worked unexpectedly well.

Albertson Declaration, page 2. Dr. Albertson also explains, that while she had an expectation regarding the likelihood of success of the shotgun cloning PCR method, she also appreciated that this particular field was relatively unpredictable. Specifically, Dr. Albertson states:

> In advance of these studies, we could not predict whether any of these techniques would yield sufficiently representative target solutions. In particular, we could not be sure that the amplification-based techniques would satisfy this requirement. Prior to carrying out these studies, I believed that the third approach, shotgun cloning followed by PCR, was the most likely to give satisfactory results. In fact, this approach failed, yielding targets prepared from human DNA that appeared incapable of hybridizing to human DNA as indicated by the low fluorescence intensity of the hybridization to these spots. ***This result demonstrates the difficulty in this field of predicting what technique will work for a particular application, based only on a theoretical understanding of the technique and/or information about its suitability for different applications.***

Albertson Declaration, pages 14-15 (emphasis added).

Whereas the amplification approach that was expected to work the best failed, the other amplification approach that the inventors tried worked unexpectedly well. Dr. Albertson states:

> Contrary to results obtained with the shotgun cloning approach, the ligation-mediated PCR approach worked unexpectedly well, producing target solutions that, when spotted and hybridized with a labeled probe, produced a signal that is essentially the same as the signal obtained from the starting polynucleotide. ***As the failure of the shotgun cloning approach demonstrates, this result could not have***

been predicted based on the available information concerning ligation-mediated PCR.

Albertson Declaration, page 15 (emphasis added).

Applicants submit that Dr. Albertson's Declaration clearly establishes that, the results embodied the method of claim 1 and the array of claim 20 were unexpected. More to the point, Applicants submit that Dr. Albertson's Declaration demonstrates "that an invention appearing [at least to the Examiner] to have been obvious in light of the prior art was not." *See Stratoflex*, 713 F.2d at 1538, 218 U.S.P.Q. (BNA) at 879. Accordingly, even if the Examiner maintains that the cited references are sufficient to establish a *prima facie* case of obviousness, Dr. Albertson's Declaration provides undeniable evidence of unexpected results. In the face of this evidence, the rejection cannot properly be maintained. Withdrawal of the § 103 rejection over Brown and Smith is therefore respectfully requested.

Brown, Smith, and Gordon

Claim 17 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Gordon et al (USPN 5,601,980). Office Action, page 7. This rejection is respectfully traversed.

Claim 17 depends ultimately from claim 1 and recites a method "wherein the target solutions are robotically spotted on the substrate." Gordon was cited for the teaching of robotic spotting. *Id.* However, Gordon fails to teach or suggest the amplification steps of claim 1, which result in approximately proportionate amplification of essentially all starting polynucleotide sequences. Moreover, Gordon is devoid of any teaching regarding the arraying of target solutions containing amplification products produced in this manner. Accordingly, the combination of Brown, Smith, and Gordon does not teach or suggest all of the elements of the claim 1, which are incorporated into claim 17 by virtue of its dependence on claim 1. Gordon also does nothing toward establishing any motivation to modify the teachings of Smith and Brown to produce the method of claim 17, much less any expectation of success in doing so.

Because the Examiner has not established any element of a *prima facie* case of obviousness of claim 17 over Smith, Brown, and Gordon, Applicants respectfully request withdrawal of the 103 rejection of claim 17.

Brown, Smith, and Stimpson

Claim 18 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Stimpson (Proc. Natl. Acad. Sci. USA (1995) 92:6370-83). Office Action, page 8. This rejection is respectfully traversed.

Claim 18 depends ultimately from claim 1, which recites the use of adaptors in the claimed amplification reaction. Claim 18 recites that "at least one strand of the adapters includes an amino group." Stimpson was cited as teaching "DNA chips (i.e., array[s]), which are constructed by using 3'-amino-labeled oligonucleotides." Office Action, page 10. However, Stimpson discloses that "DNA chips . . . were constructed by using ***presynthesized*** 3'-amine-labeled oligonucleotides." Stimpson, page 6380, col. 1. Stimpson thus fails to teach or suggest anything regarding any amplification-based method for producing target solutions for an array, much less the specific amplification steps recited in claim 1. Stimpson thus does nothing to remedy the above-noted deficiencies of Smith and Brown. Accordingly, the combination of Smith, Brown, and Stimpson does not teach or suggest all of the elements of the claim1, which are incorporated into claim 18. Stimpson also fails to provide any motivation to modify the teachings of Smith and Brown to produce the method of claim 18, much less any expectation of success in doing so.

Because the Examiner has not established any element of a *prima facie* case of obviousness of claim 18 over Brown, Smith, and Stimpson, Applicants respectfully request withdrawal of the § 103 rejection of claim 18.

Brown, Smith, and Cronin

Claims 19, 21, 22, and 24 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Cronin et al (WO 97/43450) or Pinkel et al (USPN 5,837,196). Office Action, page 8. This rejection is moot as to claim 22, which has been cancelled. As to claims 19, 21, and 24, the rejection is respectfully traversed.

Claim 19 depends from claim 1 and recites a method "wherein the target solutions comprise dimethyl sulfoxide [DMSO] at a concentration of about 20% by volume." Cronin and Pinkel were cited as teaching target solutions containing DMSO. Office Action, page 9. Cronin fails to teach or suggest the amplification steps of claim 1, which result in approximately proportionate amplification of essentially all starting polynucleotide sequences. Furthermore, Cronin is devoid of any teaching regarding the arraying of target solutions containing amplification

products produced in this manner. Cronin, like Stimpson, discloses arrays of synthetically produced oligonucleotides. Cronin, page 9, line 15 – page 10, line 29.

With respect to amplification, Pinkel teaches:

> If the tissue sample is small, so that a small amount of nucleic acids is available, amplification techniques such as the polymerase chain reaction (PCR) using degenerate primers can be used. For a general description of PCR, see, PCR Protocols, Innis et al. eds. Academic Press, 1990. In addition, PCR can be used to selectively amplify sequences between high copy repetitive sequences. These methods use primers complementary to highly repetitive interspersed sequences (e.g., Alu) to selectively amplify sequences that are between two members of the Alu family (see, Nelson et al., Proc. Natl. Acad. Sci. USA 86:6686 (1989)).

Thus, Pinkel also fails to teach or suggest the amplification steps recited in claim 1 and, consequently, neither teaches nor suggests arraying the resultant amplification products.

Thus, Cronin and Pinkel do not remedy all the deficiencies of the Brown-Smith combination. Because the cited combination fails to teach or suggest all of the elements of claim 19, Applicants respectfully request withdrawal of the § 103 rejection of claim 19 over Brown, Smith, and Cronin or Pinkel.

Claim 21 relates to a plurality of target solutions prepared by a method that includes method steps (a)-(c) of claim 1, which relate to the use of amplification to produce target polynucleotides for an array. In addition, claim 21 recites:

> d) forming target solutions from the amplification products, wherein the target solutions comprise dimethyl sulfoxide at a concentration of about 20% by volume and are suitable for application to a substrate to produce an array of polynucleotides
>
> wherein: the double-stranded polynucleotide fragments are derived from a polynucleotide library.

Thus, claim 21 incorporates the elements of claim 1 that distinguish over Brown and Smith. More specifically, the method of claim 21 employs a plurality of samples of double-stranded polynucleotide fragments, each of which is derived from a first polynucleotide. The samples are amplified to form an amplification product that is "representative of the corresponding first polynucleotide." Target solutions containing each amplification product and 20% DMSO are then formed. Cronin and Pinkel fail to teach or suggest the amplification steps of claim 21, which result

in approximately proportionate amplification of essentially all starting polynucleotide sequences. Furthermore, Cronin and Pinkel are devoid of any teaching regarding the formation of target solutions containing amplification products produced in this manner. As Cronin and Pinkel fail to remedy all the deficiencies of Brown and Smith, the cited combination does not teach or suggest the method of claim 21. Claim 24 depends from claim 21 and thus is patentable over the cited combination for at least the same reasons as claim 21. Withdrawal of the § 103 rejection of claims 21 and 24 over Brown, Smith, and Cronin or Pinkel is therefore respectfully requested.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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